REMARKS

Applicants reserve the right to prosecute non-elected subject matter in subsequent divisional applications.

Status of the Claims

Claims 1-10, 12-29, 46 and 47 have been canceled.

Claims 11 and 30-45 are currently pending.

Claims 1, 11 and 30-45 were subject to a Restriction Requirement. Applicants affirm election, with traverse, of claims 11, 31-32, 34, and 36-43, corresponding to the invention of Group II, antibodies which ***specifically bind*** to polypeptides of SEQ ID NO:1, compositions comprising the antibodies and methods of making the antibodies.

The examination of claims 30, 33, 35 and 44-45 is held in abeyance pending determination of allowability of any of the product claims from which they depend.

Amendment to the Claims

Applicants have amended claim 11 to further clarify the invention they intend to claim.

In particular, Applicants have deleted the word "human." Support for this amendment may be found in claim 11 as originally filed. No new matter is added thereby.

Claim 36 a) and 36 b) have been amended to recite ". . . having the ~~an~~ amino acid sequence of SEQ ID NO:1. . ." Use of "the" finds support in claim 11 a). Applicants assert that these amendments are done to more clearly define Applicants' invention and not for reasons related to patentability.

Claim 39 a) and 39 b) have been amended to recite ". . . having the ~~an~~ amino acid sequence of SEQ ID NO:1. . ." Use of "the" finds support in claim 11 a). Applicants assert that these amendments are done to more clearly define Applicants' invention and not for reasons related to patentability.

Obviousness Rejection under 35 U.S.C. § 103(a)

Each of the prior art rejections under 35 U.S.C. § 103(a) is based upon the combination of GenBank Accession No. AAB03214 (GI 1399101, Nussbaum, R.L.) with other references including:

1) Laxminarayan et al., (J. Biol. Chem. 1993; 268:4968-4974);

2) Palmer et al., (J. Biol. Chem. 1994; 269:3404-3410), and

3) Palmer et al., Bost et al., (Immunol. Invest. 1988; 17:577-586), Bendayan (J. Histochem. Cytochem. 1995; 43:881-886), and Ramakrishnan et al. (U.S. Pat. No. 5,817,310).

In particular, claims 36-38 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Laxminarayan et al. in view of GenBank Accession No. AAB03214;

claims 39-41 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Palmer et al. in view of GenBank Accession No. AAB03214; and

claims 11, 31-32, 34 and 42-43 stand rejected under 35 U.S.C. § 103(a) for allegedly being "unpatentable over Palmer et al. . . . in view of GenBank Accession #AAB03214 . . . and as evidenced by Bost et al. . . . and Bendayan . . . and further in view of Ramakrishnan et al.

These rejections therefore are respectfully traversed.

Applicants traverse the rejection for the reason that the Examiner has not made out a *prima facie* case of obviousness. To support an obviousness rejection under 35 U.S.C. § 103, "all the claim limitations must be taught or suggested by the prior art" and "[a]ll words in a claim must be considered in judging the patentability of that claim against the prior art." M.P.E.P. § 2143.03. In addition, "the reference teachings must somehow be modified in order to meet the claims. The modification must be one which would have been obvious to one of ordinary skill in the art at the time the invention was made." M.P.E.P. § 706.02.

At the outset Applicants note that the sequence of Nussbaum, GenBank Accession No. AAB03214 (GI 1399101), is less than 90% identical over the entire length of SEQ ID NO:1. AAB03214 is only 329 amino acids in length, and has three (3) amino acid residues differing from those of SEQ ID NO:1, resulting in AAB03214 sharing only 326 identical amino acid residues with SEQ ID NO:1 over the entire length of SEQ ID NO:1. SEQ ID NO:1 is 372 amino acids in length (specification at page 13 lines 18-20; Sequence Listing pages 52-53).

The proper calculation for the determination of percent sequence identity of one sequence to another, is well known to one of ordinary skill in the art. To illustrate, a comparison of AAB03214 to SEQ ID NO:1, the calculation is as follows:

> (Length of AAB03214) minus (number of amino acids not identical to SEQ ID NO:1) divided by the total length of SEQ ID NO:1 times 100 equals percent identity.

Comparing AAB03214 to SEQ ID NO:1:

329-3 / 372 x 100 = 87.63% identity to SEQ ID NO:1

AAB03214 lacks amino acids 1-44 of SEQ ID NO:1 and one of ordinary skill in the art would not expect AAB03214 to have phophatidylinositol 4,5-bisphosphate 5-phosphatase activity, as the IPPc catalytic domain is incomplete at the 5' end of AAB03214. One of ordinary skill in the art would conclude that, more likely than not that the sequence of Nussbaum would not have 5-phosphatase activity (see Attachment H, *infra*). Thus, the sequence of Nussbaum does not teach each and every limitation of SEQ ID NO:1 or the claimed 90% variants of SEQ ID NO:1 and lacks phophatidylinositol 4,5-bisphosphate 5-phosphatase activity.

Thus, the sequence of AAB03214 (Nussbaum) is not a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1 and one of ordinary skill in the art would conclude that the sequence of Nussbaum lacks phophatidylinositol 4,5-bisphosphate 5-phosphatase activity, contrary to the position of the Office (Office Action of March 16, 2003, page 6). Furthermore, not only is Nussbaum deficient 44 amino acids in comparison to SEQ ID NO:1, it also lacks an antigenic determinant found in SEQ ID NO:1. Examination of Attachment A, an alignment of SEQ ID NO:1 (638789CD1) with the sequence of Nussbaum (gi1399101) indicates both the additional 44 amino acids within SEQ ID NO:1 and the three amino acids differing between the two sequences.

Applicants provide herewith Attachments B (AAB03214, GI 1399101) and C (638789CD1 = SEQ ID NO:1) to assist the Examiner in visualizing the antigenic determinants identified in each sequence by DNASTAR, a sequence analysis software program (see, specification, page 50, lines 14-29, Example XI). Applicants have inserted at the 5' end of AAB03214 (GI 1399101) 44 "X" residues

to provide a residue by residue comparison along the entire length of each sequence. What is readily apparent is that SEQ ID NO:1 has an antigenic determinant at amino acid residues 37-48 which is not present in AAB03214 (GI 1399101). Thus, an antibody which specifically binds to SEQ ID NO:1 or variants thereof at this "epitope," residues, 37-48 of SEQ ID NO:1, would not be expected by one of ordinary skill in the art to bind to the sequence of Nussbaum, as no such epitope is taught by Nussbaum.

Additionally, there is no suggestion in the art to modify the sequence of AAB03214. Applicants note that AAB03214 is derived from ESTs, GenBank Accession Number H09678 and R18994 (see AAB03214). As such, neither EST suggests the epitope between residues 37-48 of SEQ ID NO:1 to which an antibody would specifically bind to AAB03214.

Therefore, AAB03214 does not teach all the claimed limitations, can neither anticipate SEQ ID NO:1 nor 90% variants thereof in its present form, and there is no suggestion in the art that antibodies made to AAB03214 would render obvious the claims of the instant invention.

Claims 36 and 39 contain all the limitations of claim 11

Contrary to the position of the Office, Applicants note that claim 36, as a dependent claim depending from claim 11, contains all the limitations of claim 11, see 37 C.F. R. 1.75(c). In other words, all claim limitations of parent claim 11 are incorporated into dependent claim 36 and claims which depend therefrom. Thus, claims 36-38 are no longer limited to human antibodies.

Additionally, claims 36 a) and b) have been amended to recite " . . . having ~~an~~ the amino acid sequence . . ." Thus, the polypeptide of Nussbaum, AAB03214, does not meet the limitation of method claim 36 as to the polypeptide which would be used to immunize. This amendment was done to further clarify the instant invention and not for reasons related to patentability. Therefore, claims 36-38 are not rendered obvious based on Laxminarayan et al. in view of GenBank Accession No. AAB03214.

Contrary to the position of the Patent Office, Applicants note that claim 39, as a dependent claim depending from claim 11, contains all the limitations of claim 11, see 37 C.F. R. 1.75(c). In other words, all claim limitations of parent claim 11 are incorporated into dependent claim 39 and claims which depend therefrom. Thus, claims 39-41 are no longer limited to human antibodies.

Additionally, claims 39 a) and b) have been amended to recite " . . . having ~~an~~ the amino acid sequence . . ." Thus, the polypeptide of Nussbaum, AAB03214, does not meet the limitation of method claim 39 as to the polypeptide which would be used to immunize. This amendment was done to further clarify the instant invention and not for reasons related to patentability. Therefore, claims 39-41 are not rendered obvious based on Palmer et al. in view of GenBank Accession No. AAB03214.

Antibodies taught by Laxminarayan et al. and Palmer et al. do not **specifically** bind to the polypeptides recited in the claims

The Office asserts that the only way to select for a subset of antibodies which bind the protein of interest and not bind a closely related protein would be using a screening strategy neither taught in the specification nor claimed (Office Action of August 26, 2003, page 8). It is Applicants position that antibodies which bind the proteins of interest are only those antibodies which specifically bind SEQ ID NO:1 and variants thereof. Such antibody screening procedures are routine in the art, and do not constitute undue experimentation which would render Applicants' invention not enabled. See, e.g., *In re Wands* 8USPQ 2d 1400 (CAFC 1988).

Furthermore, the Examiner has asserted that "arguing that "specific binding" excludes binding of related proteins which share epitopes with the protein of interest argues limitations . . . that are contrary to both the art-recognized usage of the term "specific binding," and the usage of the term in the specification as filed" (Office Action of August 26, 2003, page 8). Applicants' own definition of 'specific binding' on page 11 at lines 21-27 refers only to the "interaction between a protein or peptide and an agonist, an antibody, or an antagonist" (specification, page 11, lines 21-22). Although the specification discloses that this interaction "is dependent upon the presence of a particular structure (e.g., the antigenic determinant or epitope) of the protein recognized by the binding molecule" (specification, page 11, lines 22-24), nowhere does the specification state that specificity of an antibody for a polypeptide is the **same** as specificity of an antibody for an epitope of that polypeptide. The specification provides an example of an antibody that is specific for an epitope:

> For example, if an antibody is specific for epitope "A", the presence of a polypeptide containing the epitope A (or free, unlabeled A) in a reaction containing labeled "A" and the antibody will reduce the amount

> of labeled A that binds to the antibody. (specification, page 11, lines 24-27)

This example deals only with an antibody that is "specific for an epitope"; it is not an example of an antibody which "specifically binds to a **polypeptide**."

An antibody which "specifically binds" to a polypeptide binds **specifically** to that **polypeptide**. The interaction of the antibody and the polypeptide is dependent on the epitope bound by the antibody, but this does not mean that an antibody that is specific for an epitope on the polypeptide is the same thing as an antibody that specifically binds to the polypeptide. Specificity for an epitope of a polypeptide is distinct from specificity for the polypeptide considered as a whole. The antibodies recited by the claims **specifically** bind to the recited polypeptides. Since Laxminarayan et al. and Palmer et al. teach antibodies which bind to polypeptides other than those recited by the claims, the antibodies taught by Laxminarayan et al. and Palmer et al. do not **specifically** bind to the recited polypeptides. The antibodies taught by Laxminarayan et al. and Palmer et al. are excluded from the claimed antibodies because they do not **specifically** bind to the polypeptides recited in the claims.

Bost et al. and Bendayan have been misconstrued by the Office

The Examiner misstates the conclusions of the references of Bost et al. and Bendayan. The antibody of Bost et al. specifically bound to two different polypeptides that shared a similar **epitope**, but not to polypeptides lacking this epitope. Bost et al. **did not** teach that their antibody was specific for one of the polypeptides, but only that it was specific for the epitope. In contrast, the claimed antibodies specifically bind to the recited polypeptides.

Similarly, Bendayan teaches that an antibody that was originally thought to be specific for human proinsulin also bound to proinsulin from other species and to glucagon from several species. Bendayan does not contradict the fact that the antibody is specific; however, this reference indicates that the antibody is not specific only for human proinsulin. The antibody of Bendayan is specific for human proinsulin, rat proinsulin, human glucagon, and bovine and porcine insulin and glucagon. In contrast, the antibodies recited by the claims specifically bind to the recited polypeptides. Since Bost et al. and Bendayan teach antibodies other than those recited by the claims, the antibodies taught by Bost et al. and Bendayan do not **specifically** bind to the recited polypeptides and are not encompassed in

the claimed subject matter.

The claimed antibodies bind **specifically** to SEQ ID NO:1 and variants thereof

Applicants have pointed out the distinction between the "specific binding" of an antibody to a particular **epitope**, and the "specific binding" of an antibody to a particular **polypeptide**. Furthermore, Applicants have indicated how this distinction is supported by the specification. An antibody which specifically binds to a particular epitope would bind to any polypeptide having that epitope. However, an antibody which specifically binds to a particular polypeptide, such as the antibodies recited in the claims, would not specifically bind to render obvious either "other polypeptides" or antibodies to the "other polypeptides."

The Examiner has improperly rejected claims 11, 21-32, 34 and 36-43 based on the alleged anticipation as taught by the partial polypeptide sequence of Nussbaum in view of Laxminarayan et al. and in view of Palmer et al. and further in view of Ramakrishnan et al. because the Examiner has insisted that the phrase "specific binding" be interpreted such that an antibody is specific for an **epitope**. However, this ignores the language of the claims, which recite that the claimed antibodies "specifically bind" to particular polypeptides, **not** to particular epitopes.

Thus, the Office Action has not made a *prima facie* showing that the partial polypeptide sequence of Nussbaum in view of Laxminarayan et al. and in view of Palmer et al. and further in view of Ramakrishnan et al. anticipate the claimed antibodies. The Office Action has not explained how the teachings of Nussbaum in view of Laxminarayan et al. and in view of Palmer et al. and further in view of Ramakrishnan et al., Bost et al., and Bendayan, could be modified in order to arrive at the claimed subject matter. Therefore, the Office has not met the requirements for a *prima facie* showing of obviousness under 35 U.S.C. § 103. For at least the above reasons, this rejection should be withdrawn.

Indefiniteness Rejection under 35 U.S.C. § 112, second paragraph

Claim 31 is rejected for allegedly failing to provide antecedent basis for the recitation of "chimeric antibody" and "humanized antibody" because claim 11, from which claim 31 depends limits the nature of the antibody to a "human" antibody" (Office Action of August 26, 2003, page 3, section

7). Applicants traverse this rejection.

Applicants have amended claim 11 to remove recitation of "human." Therefore, the issue of indefiniteness of claim 31 regarding the "human antibodies" recited in claim 11 is moot. Withdrawal of this rejection is respectfully requested.

Written Description Rejection under 35 U.S.C. § 112, first paragraph

Claims 11, 31-32, 34 and 36-43 have been rejected under 35 U.S.C. § 112, first paragraph, allegedly because the claimed subject matter "was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention" (Office Action of August 26, 2003, page 3, section 9). Specifically, the Office has asserted that Applicants' specification "does not appear to have disclosed the relevant, identifying characteristics shared by the polypeptide of SEQ ID NO:1 and sequence variants thereof necessary for antibody binding to the members of the genus of variant polypeptides (i.e., Applicant has not defined an antibody epitope)" (Office Action of August 26, 2003, page 4, section 9). Applicants traverse this rejection.

It is Applicants' position that the amino acid sequence of 90% variants of SEQ ID NO:1 having phosphatidylinositol 4,5-bisphosphate 5-phosphatase activity is adequately described in the specification as filed since the structure of SEQ ID NO:1 is fully defined. The art-recognized methods of determining percent identity of amino acid sequences, including SEQ ID NO:1 variants and the art-recognized methods to determine phosphatidylinositol 4,5-bisphosphate 5-phosphatase activity, as taught in the instant specification, e.g., Example X, page 50 lines 9-12, are well known to one of ordinary skill in the art. Additionally, the instant specification teaches the presence of the well defined structural characteristics of SEQ ID NO:1 polypeptides and variants thereof, as taught in the instant specification, e.g., page 2 lines 5-9; page 13 lines 27 to 28, including the two potential catalysis or binding sites at N104-D123 and D181-K200. Therefore, it is Applicants position that claims 1, 31-32, 34 and 36-43 meet the written description requirements of 35 U.S.C. § 112, first paragraph.

The requirements necessary to fulfill the written description requirement of 35 U.S.C. § 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)
>
> . . . Mention of representative compounds encompassed by generic claim language ***clearly is not required by Section 112 or any other provision of the statute***. But, where no explicit description of a generic invention is to be found in the specification...mention of representative compounds may provide an implicit description upon which to base generic claim language. *In re Robins*, 429 F.2d 452, 456-57, 166 USPQ 552, 555 (CCPA 1970) [emphasis added]
>
> . . . [I]t has been consistently held that the naming of one member of such a group is not, in itself, a proper basis for a claim to the entire group. However, ***it may not be necessary to enumerate a plurality of species if a genus is sufficiently identified in an application by 'other appropriate language.'*** *In re Grimme*, 274 F.2d 949, 952, 124 USPQ 499, 501 (CCPA 1960) [emphasis added]

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that:

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., ***complete or partial structure***, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. ***If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.*** [emphasis added] [footnotes omitted]

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

I. The specification provides an adequate written description of the claimed "variants" of SEQ ID NO:1

The subject matter encompassed by Claims 11, 31-32, 34 and 36-43 are either disclosed by the specification or conventional or well known to one skilled in the art.

Independent claim 11 as amended recites "An isolated antibody that specifically binds to a polypeptide selected from the group consisting of: a) a polypeptide comprising the amino acid sequence of SEQ ID NO:1, and b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1 and having phosphatidylinositol 4,5-bisphosphate 5-phosphatase activity." The Examiner's position is based upon the theory that the specification provides an adequate written description of SEQ ID NO:1 since the structure of SEQ ID NO:1 is fully defined . . . the disclosure describes the genus of antibodies to SEQ ID NO:1 in sufficient detail such that the artisan can reasonably conclude that Applicant had possession of the genus of antibodies to the polypeptide of SEQ ID NO:1" (Office Action of August 26, 2003 at page 3).

The Examiner continues, alleging that the specification lacks an adequate written description of the much more extensive genus of antibodies which would bind to "*any* member of a genus of naturally-occurring polypeptides related to SEQ ID NO:1 by 90% or more amino acid sequence identity, so long as the polypeptide has phosphatidylinositol 4,5-bisphosphate 5-phosphatase activity" (August 26, 2003 at page 3, Emphasis in original). Applicants strongly disagree with this position.

Such a position ignores that the antibodies recited in claim 1) ***are*** described in terms of their structure. That is, the claimed antibodies specifically bind polypeptides which are "***at least 90% identical to the amino acid sequence of SEQ ID NO:1 and having phophatidylinositol 4,5-bisphosphate 5-phosphatase activity***." The structure of SEQ ID NO:1 is provided in the specification, for example, at pages 52-53 of the Sequence Listing and Figures 1A, 1B, 1C, 1D, 1E, 1F and 1G for SEQ ID NO:1. The phrases "percent identity" or "% identity" as well as methods for determining such identity are well known to the skilled artisan. Claim 1, as previously amended, does not encompass ***any*** antibody to any peptide or protein with altered sequence, rather only those antibodies that ***specifically*** bind to peptides or proteins limited to those having at least 90% amino acid sequence identity to SEQ ID NO:1 and having phophatidylinositol 4,5-bisphosphate 5-phosphatase activity.

Applicants submit that this description is sufficient to describe the claimed genus based on the disclosure of the single species, SEQ ID NO:1, for reasons stated in the USPTO's own training

materials for implementation of the Written Description Guidelines under 35 USC § 112, first paragraph. In the "Synopsis of Application of Written Description Guidelines" (USPTO Website www.uspto.gov, March 1, 2000), at page 53 of these guidelines, a claim to "A protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A → B" is considered to meet the written description requirements because:

> --- procedures for making variants of SEQ ID NO:3 are conventional in the art and an assay is described which will identify all other proteins having the claimed catalytic activity. Moreover, procedures for making variants of SEQ ID NO:3 which have 95% identity to SEQ ID NO:3 and retain its activity are conventional in the art.

The Guidelines further state:

> The single species disclosed (SEQ ID NO:3) is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO:3 which are capable of the specified catalytic activity.

Thus, Applicants submit that just as variants of polypeptides which are at least 95% identical to a given species, i.e., SEQ ID NO:1 in the instant application, meet the USPTO's own Written Description Guidelines, so too do polypeptide variants at least 90% identical to SEQ ID NO:1 and having phophatidylinositol 4,5-bisphosphate 5-phosphatase activity fulfill the USPTO's own Written Description Guidelines. Therefore, the specification, as filed provides adequate written description support for a polypeptide having at least 90% sequence identity to SEQ ID NO:1 and having phophatidylinositol 4,5-bisphosphate 5-phosphatase activity as established by the USPTO's "Synopsis of Application of Written Description Guidelines."

A detailed description of the chemical and structural features of SEQ ID NO:1 which contributes to the characterization of SEQ ID NO:1 and other related proteins related to the 5-phosphatase protein phosphatase family are provided, for example, at page 13 lines 18 to 28 and Figures 2A, 2B, 2C, 2D and 2E. Ninety percent variants of the polypeptides specifically bound by the claimed antibodies are described, for example, at page 14, lines 4-8.

When provided with the detailed description as noted above, one of ordinary skill in the art "would have understood the inventor to be in possession of the claimed invention at the time of filing."

That is, one of ordinary skill in the art would recognize polypeptide sequences bound by the claimed antibodies which are variants at least 90% identical to SEQ ID NO:1 and having phophatidylinositol 4,5-bisphosphate 5-phosphatase activity. Given a polypeptide sequence, it would be routine for one of skill in the art to recognize whether it was a variant of SEQ ID NO:1, to determine the percent identity to SEQ ID NO:1 of the variant, and analyze for phophatidylinositol 4,5-bisphosphate 5-phosphatase activity. Accordingly, the specification provides an adequate written description of the recited variants of SEQ ID NO:1 having phophatidylinositol 4,5-bisphosphate 5-phosphatase activity.

II. The Examiner Argues Limitations Not Claimed

The Examiner asserts that "adequate identification of one or more ***epitopes*** shared by members of a genus of variant polypeptide structures is essential to describing a distinguishing identifying characteristic sufficient to show that Applicant was in possession of the claimed genus of antibodies." The Examiner concludes that "when claims are not limited to either a defined polypeptide sequence, or to [*sic*] polypeptides encompassing sequence variation but sharing a defined antibody epitope, the ordinary artisan would not conclude that there was sufficient structural constrains . . . to show that Applicant was in possession of the genus" (Office Action, August 26, 2003; page 4). The Examiner's arguments focus on the specificity of antibodies for ***epitopes***, even though the claimed antibodies are not limited by specific binding to epitopes. The claims recite antibodies which specifically bind to **polypeptides**. Therefore, the Examiner's arguments cannot be applied to the claimed subject matter.

In addition, the Applicants' arguments are not inconsistent with common understanding of antibody-antigen interactions. Applicants acknowledge that the binding of an antibody to an antigen is dependent on the specific epitope to which the antibody binds. Applicants also acknowledge that this dependency is commonly understood in the art, as demonstrated by the Illustrated Dictionary of Immunology (J.M. Cruse and R.E. Lewis, eds. , CRC Press, Inc., Boca Raton FL, 1995, pages 18-19, 22-23, and 102-103) and Van Regenmortel (Methods: A Companion to Methods in Enzymology, 1996, 9:465-472), each cited by the Examiner. However, the claimed antibodies are not limited by specific binding to an epitope. Even if specific binding of an antibody to a polypeptide depends on the specific binding of that antibody to an epitope of that polypeptide, this does not mean that specificity for

an epitope is the same thing as specificity for a polypeptide. The claims recite antibodies which specifically bind to the recited polypeptides.

The Examiner has ignored the claim recitation of "specifically binds." Independent claim 11 recites "[a]n isolated antibody which specifically binds to a polypeptide comprising the amino acid sequence of SEQ ID NO:1." The present claims recite an antibody which "**specifically binds**" a polypeptide comprising SEQ ID NO:1. The ordinary meaning of "specific" is "pertaining to, characterizing, or distinguishing a species." (Attachment D, see the attached dictionary definition of specific).

Thus, an antibody which specifically binds a polypeptide comprising SEQ ID NO:1 will be able to distinguish the SEQ ID NO:1 polypeptide from other polypeptides. Hence, the skilled artisan would understand the distinction between specificity for an epitope and specificity for a polypeptide, and the Examiner has not provided any evidence to show otherwise.

III. The specification provides an adequate written description as required by law

Applicants submit that case law in the area of the written description requirement of 35 U.S.C. 112, first paragraph is clear with regard to the details considered sufficient to describe a claimed genus:

> . . . Mention of representative compounds encompassed by generic claim language ***clearly is not required by Section 112 or any other provision of the statute***. But, where no explicit description of a generic invention is to be found in the specification . . . mention of representative compounds may provide an implicit description upon which to base generic claim language. *In re Robins*, 429 F.2d 452, 456-57, 166 USPQ 552, 555 (CCPA 1970) [emphasis added]

> . . . [I]t has been consistently held that the naming of one member of such a group is not, in itself, a proper basis for a claim to the entire group. However, ***it may not be necessary to enumerate a plurality of species if a genus is sufficiently identified in an application by 'other appropriate language.'*** *In re Grimme*, 274 F.2d 949, 952, 124 USPQ 499, 501 (CCPA 1960) [emphasis added]

The specification sets forth a description of the claimed antibodies which specifically bind to polypeptide variants using "other appropriate language" as indicated above in connection with the remarks regarding an amino acid sequence at least 90% identical to the amino acid sequence of SEQ

ID NO:1 and having phophatidylinositol 4,5-bisphosphate 5-phosphatase activity." The claimed variants have been described in terms of their relationship to the chemical structure of SEQ ID NO:1 and structural requirements at, for example, pages 52-53 of the Sequence Listing; Figures 1A, 1B, 1C, 1D, 1E, 1F and 1G; page 13, lines 18-28 and Figures 2A, 2B, 2C, 2D and 2E. The specification provides a means of identifying functional variants having 90% sequence identity with SEQ ID NO:1 and having phophatidylinositol 4,5-bisphosphate 5-phosphatase activity at, for example, page 14, lines 4-8 and the assay taught in Example X (specification, page 50 lines 9-12).

Additionally, the specification teaches binding/catalytic domains known to function in Mg(2+)-dependent/Li(+)-sensitive enzymes (specification, page 2 lines 1-3). Such domains are known by one of ordinary skill in the art to be an identifying functional characteristic of 5-phosphatase proteins, including SEQ ID NO:1 as taught in the specification (page 13 lines 24-28). Thus, the skilled artisan would understand that in order for variants of SEQ ID NO:1 to have phophatidylinositol 4,5-bisphosphate 5-phosphatase activity, functional variants of SEQ ID NO:1 would retain the catalysis/binding domains.

Applicants therefore submit that the "genus is sufficiently identified in [the instant] application by 'other appropriate language'" as stated in *In re Grimme*, 274 F.2d 949, 952, 124 USPQ 499, 501 (CCPA 1960). Furthermore, Applicants submit that "a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing" as stated in the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001. Accordingly, claims 11, 31-32, 34 and 36-43 meet the statutory requirements for written description under 35 U.S.C. 112, first paragraph.

IV. Conclusion

The Office Action failed to base its written description inquiry pertinent to the present claims in view of their scope. In particular, the subject matter of the claims of the instant application is defined in terms of the chemical structure of SEQ ID NO:1. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus of antibodies which specifically bind to the polypeptides of SEQ ID NO:1 as defined by the present claims is adequately described, as evidenced by specific passages of the

specification as set forth above. Furthermore, the Examiner has applied to the subject application a written description standard that has no basis in the law.

For at least the above reasons it is believed that Claims 11, 31-32, 34 and 36-43 meet the written description requirement of 35 U.S.C. § 112, first paragraph. It is therefore requested that this rejection be withdrawn.

Enablement Rejection under 35 U.S.C. § 112, first paragraph

Claims 11, 31-32, 34 and 36-43 have been rejected under 35 U.S.C. § 112, first paragraph, allegedly because the claimed subject matter "while being enabling for antibodies in various forms which bind SEQ ID NO:1, does not reasonably provide enablement for antibodies which bind a polypeptide comprising "a naturally-occurring amino acid sequence having at least 90% sequence identity to SEQ ID NO:1 and having phophatidylinositol 4,5-bisphosphate 5-phosphatase activity" (Office Action of August 26, 2003, page 5, section 10). Applicants respectfully traverse this rejection.

At the outset, the use of the antibodies which specifically bind the recited "variants" of SEQ ID NO:1 should not be at issue. That is, these antibodies have the same uses as an antibody which specifically binds to a polypeptide comprising the amino acid sequence of SEQ ID NO:1. For example, the skilled artisan could use the claimed antibodies to purify a protein having an amino acid sequence comprising a variant sequence of SEQ ID NO:1 (See the specification, for example, at page 51, lines 1-11). In another use, antibodies to variants of the amino acid sequence of SEQ ID NO:1 can be used for drug screening purposes (See the specification, for example, at page 42, lines 17-20). Note lines 19-20, which state that "antibodies can be used to detect the presence of any peptide which shares one or more antigenic determinants with PBPP." Additionally, antibodies which specifically bind to variants of SEQ ID NO:1 can be used, for example, in 2D-PAGE analysis for expression profiling related to toxicology testing, drug discovery and disease diagnosis. Thus, Applicants submit that the skilled artisan would readily know how to use antibodies to a "variant" of the sequence of SEQ ID NO:1 and that undue experimentation would not be required.

Moreover, there should be no issue with how to make the antibodies *per se*. Methods for making antibodies are well known in the art, and are also described in the specification at, for example,

page 50, lines 14-29. The same methods for producing antibodies to polypeptides which comprise SEQ ID NO:1 could be used to make antibodies which specifically bind "variants" of SEQ ID NO:1.

Thus, the rejection appears to based on the presumption that one could not make the claimed antibodies because one would allegedly not be able to make the recited "variants" of SEQ ID NO:1 *per se*, which in turn are used to produce antibodies which specifically bind those proteins. However, this presumption is incorrect.

As set forth in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

> The first paragraph of § 112 requires nothing more than **objective enablement**. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

The Examiner's attention is also directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078, enclosed herewith). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.)

Claim 11 recites, *inter alia*, antibodies which specifically bind to "a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1 and having phophatidylinositol 4,5-bisphosphate 5-phosphatase activity." In accordance with Brenner et al., naturally occurring molecules may exist which could be characterized as PBPP-like proteins and which have as little as 30% identity over at least 150 residues to SEQ ID NO:1. The

"90% variants" recited by the present claims have a variation that is far less than that of all potential PBPP-like proteins related to SEQ ID NO:1, i.e., those PBPP-like proteins having as little as 30% identity over at least 150 residues to SEQ ID NO:1. Therefore, one would expect the SEQ ID NO:1 variants recited by the present claims to have the functional activities of a PBPP-like protein.

The Office Action mailed August 26, 2003 alleges that the specification failed to teach those polypeptide variants which retain phophatidylinositol 4,5-bisphosphate 5-phosphatase activity (Office Action of August 26, 2003, page 5). However, a patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 9029 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986); MPEP § 2164.01.

It is Applicants' position that one of ordinary skill in the art knew and understood the importance of the enzymatic activity catalytic domains within 5-phosphatases and that such knowledge was well known and well established prior to June 27, 1997, Applicants' priority date. Such domains would be understood by one of ordinary skill in the art to be retained within variants of SEQ ID NO:1 such that the variants retained phophatidylinositol 4,5-bisphosphate 5-phosphatase activity.

Examination of a recent BLASTP analysis of SEQ ID NO:1 verse genpept137 (Attachment E) reveals that SEQ ID NO:1 is 100% identical to GI 13279338, GenBank Accession No. AAH04362 (Strausberg,R.L., et al., Attachment F). The IPPc catalytic domain in SEQ ID NO:1/AAH04362 resides from residue R12 to residue L325 (Attachment G). Additionally, the specification teaches the presence of binding/catalyic motifs in a type II polyphosphate 5-phosphatase, page 2 lines 4-9, and within SEQ ID NO:1, page 13 lines 20-28. One of ordinary skill in the art understands that such domains are indicative of function and are involved in 5-phosphatase activity. Thus, not only was the IPPc catalytic domain known to function in Mg(2+)-dependent/Li(+)-sensitive enzymes (specification, page 2 lines 1-3) for many years prior to Applicants' discovery of SEQ ID NO:1, as encoded by SEQ ID NO:2, the skilled artisan would understand that in order for variants of SEQ ID NO:1 to have phophatidylinositol 4,5-bisphosphate 5-phosphatase activity, functional variants of SEQ ID NO:1 would retain the IPPc domain.

The Office's attention is directed to Attachment H, which illustrates the conserved domains within GenBank Accession No. AAB03214 (Nussbaum, R.L.). What is readily apparent is that the

IPPc domain is incomplete at the 5' end of AAB03214. One of ordinary skill in the art would conclude that, more likely than not that the sequence of Nussbaum would not have 5-phosphatase activity. Thus, the sequence of Nussbaum is not encompassed by the claimed 90% variants of SEQ ID NO:1 and lacks phophatidylinositol 4,5-bisphosphate 5-phosphatase activity.

Therefore, based on well known and well-established characteristics and properties of 5-phosphatase proteins together with the structure of SEQ ID NO:1, the teaching in the specification of catalysis or binding domains which characterize 5-phosphatase proteins, the presence of the IPPc domain within SEQ ID NO:1, and the art recognized function of proteins having IPPc catalytic domains, i.e., 5-phosphatase activity, one of ordinary skill in the art would be enabled to practice the invention as claimed and to recognize variants of SEQ ID NO:1 having phophatidylinositol 4,5-bisphosphate 5-phosphatase activity.

In general, antibody production is an empiric process that necessarily requires immunization with particular putative immunogenic fragments and subsequent screening of the products (e.g., antisera, hybridoma supernatants, recombinant immunoglobulin libraries or panels of highly specific binding reagents) to identify those fragments capable of giving rise to antibodies having the requisite specificity and affinity for the target antigen (in the present case, SEQ ID NO:1 and variants therefore). This procedure is routine in the art, and does not constitute undue experimentation which would render Applicants' invention not enabled. See, e.g., *In re Wands* 8USPQ 2d 1400 (CAFC 1988). Indeed, the generation of antibodies necessarily involves genetic rearrangement in reaction to immunogenic challenge; that rearrangement process, and the resulting products, are inherently variable and constitute the basis for the remarkable ability of the mammalian immune system to respond to novel antigenic challenges with a high degree of specificity. Therefore, the process of challenge and screening are an inherent and unavoidable part of identifying antibodies, both polyclonal and monoclonal, which specifically bind to an identified target antigen, and cannot be considered undue experimentation.

The Examiner relies on Abaza et al., and Li et al. to support the enablement rejection. However, none of the cited documents supports the Examiner's position.

The Examiner asserts that the specification allegedly provides insufficient guidance as to the making of the instantly recited polypeptides and antibodies based on the Abaza et al. teaching that "single amino acid changes outside the antigenic site on a protein effect [*sic*] antibody binding. (Office

Action mailed August 26, 2003, page 6, 5th ¶). The Examiner concludes that "it would require undue experimentation to make and use the antibodies to variants of the polypeptide of SEQ ID NO:1." (Office Action mailed August 26, 2003, page 6, 8th ¶.)

The Examiner misapprehends the plain meaning of the claims. The claims are directed to isolated antibodies which specifically bind to the polypeptide, if the antibody doesn't specifically bind, then it is not encompassed by the claim.

The specification discloses methods to make antibodies which specifically bind to a polypeptide having **any** particular amino acid sequence (e.g., at page 27 line 9 through page 28 line 24 and page 50 lines 14-29). Given the information provided by SEQ ID NO:1, one of skill in the art would be able to routinely obtain antibodies which specifically bind to "a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to an amino acid sequence of SEQ ID NO:1 and having phophatidylinositol 4,5-bisphosphate 5-phosphatase activity." For example, an animal could be immunized with a polypeptide having a particular naturally occurring amino acid sequence at least 90% identical to SEQ ID NO:1 and having phophatidylinositol 4,5-bisphosphate 5-phosphatase activity, antibodies could be isolated from the animal, and the antibodies could be screened to identify antibodies which specifically bind to the polypeptide.

The Office Action mailed August 26, 2003 attempts to provide further support for this rejection by citing Li et al. (Proc. Natl. Acad. Sci. USA (1980) 77:3211-3214), which teaches "dissociation of immunoreactive from other biological activities when constructing analogs" (Office Action mailed August 26, 2003, page 6, 5th ¶). The Patent Office seems to be implying that the claimed antibodies are not enabled because it has not been shown that an antibody which specifically binds to one naturally occurring variant of SEQ ID NO:1 also binds to all other naturally occurring variants of SEQ ID NO:1, and to SEQ ID NO:1 itself. Such a showing is not necessary because the claims are not directed to antibodies which specifically bind to every single one of the recited polypeptides. The claims are directed to antibodies which specifically bind to any one of the recited polypeptides. Thus, one of skill in the art could use the methods disclosed in the specification to make and use antibodies which specifically bind to one particular naturally occurring variant of SEQ ID NO:1, and it would be irrelevant whether the antibodies specifically bound to any of the other recited polypeptides.

Further, the Examiner misapplies the law. To enable the claimed invention, Applicants need

only disclose information sufficient to permit one of ordinary skill in the art to make and use the invention as claimed, without *undue* experimentation. It is the Examiner's burden to establish that undue experimentation would be necessary to carry out Applicants' invention. *In re Angstadt*, 190 USPQ 214, 219 (CCPA 1976).

It appears that a quantum of **working examples** is being required by the Examiner (Office Action of August 26, 2003, page 6, 3rd ¶). There is no such requirement under the law to provide "working examples." As set forth in *In re Borkowski,* 164 USPQ 642, 645 (CCPA 1970) (footnote omitted):

> However, as we have stated in a number of opinions, a specification need not contain a working example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation.

See also M.P.E.P. 2164.02 as follows:

> Compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed. An example may be "working" or "prophetic"... A prophetic example describes an embodiment of the invention based on predicted results rather than work actually conducted or results actually achieved.

Thus, there is no requirement under the law to provide "working examples" of what is claimed. Rather, one looks to whether the specification provides a description of how to make what is claimed. The present specification provides the requisite description.

Contrary to the standard set forth in Marzocchi and Borkowski, the Examiner has failed to provide any ***reasons*** why one would doubt that the guidance provided by the present specification would enable one to make and use the 90% variants of SEQ ID NO:1. Hence, a *prima facie* case for non-enablement has not been established for the 90% variants of SEQ ID NO:1. For at least the above reasons, withdrawal of the enablement rejections under 35 U.S.C. § 112, first paragraph, is respectfully requested.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding objections/rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned at the number listed below.

Please charge Deposit Account No. **09-0108** in the amount of **$420.00** as set forth in the enclosed fee transmittal letter. If the USPTO determines that an additional fee is necessary, please charge any required fee to Deposit Account No. 09-0108.

Respectfully submitted,
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Attachment(s):
Brenner et al., Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078.
A: ClustalW alignment, SEQ ID NO:1 (638789CD1) vs. Nussbaum (AAB03214, GI 1399101).
B: DNASTAR analysis of AAB03214 (GI 1399101).
C: DNASTAR analysis of SEQ ID NO:1 (638789CD1).
D: Definition for "specific", "The American Heritage Dictionary, 1985, Boston, p. 1173.
E: BLASTP results for SEQ ID NO:1 verse genpept137.
F: GenBank entry for GenBank Accession No. AAH04362 (Strausberg,R.L.., et al.).
G: Identification of Domain Structures in GenBank Accession No. AAH04362/SEQ ID NO:1.
H: Identification of Domain Structures in GenBank Accession No. AAB03214, GI 1399101 (Nussbaum).